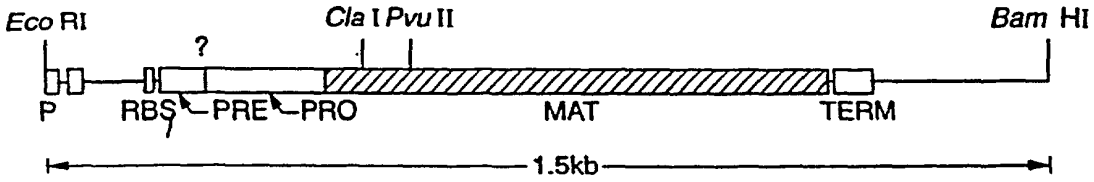


FIG._1A

TOE2TO"D80892S0

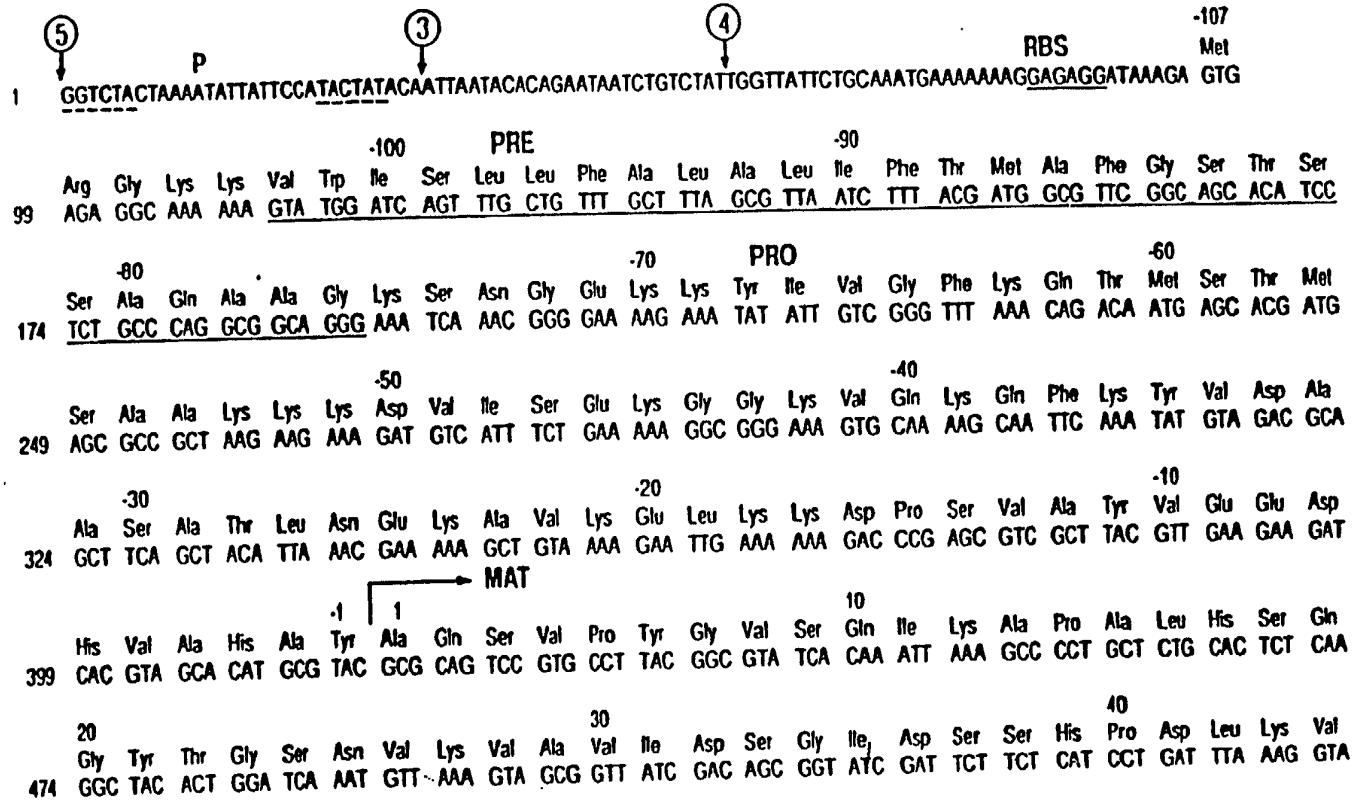


FIG._1B - 1

TOE2TO"080892760

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                                  50                                                  Pro  Asn                 60   Asp
     Ala  Gly  Gly  Ala  Ser  Met  Val  Pro  Ser  Glu  Thr  Asn  Pro  Phe  Gln  Asp  Asn  Asn  Ser  His  Gly  Thr  His  Val  Ala
549  GCA  GGC  GGA  GCC  AGC  ATG  GTT  CCT  TCT  GAA  ACA  AAT  CCT  TTC  CAA  GAC  AAC  AAC  TCT  CAC  GGA  ACT  CAC  GTT  GCC

     70                                                  80                                                  Ser  Ala  90
     Gly  Thr  Val  Ala  Ala  Leu  Asn  Asn  Ser  Ile  Gly  Val  Leu  Gly  Val  Ala  Pro  Ser  Ala  Ser  Leu  Tyr  Ala  Val  Lys
624  GGC  ACA  GTT  GCG  GCT  CTT  AAT  AAC  TCA  ATC  GGT  GTA  TTA  GGC  GTT  GCG  CCA  AGC  GCA  TCA  CTT  TAC  GCT  GTA  AAA

                  Asp  Ala  100                                                 110
     Val  Leu  Gly  Ala  Asp  Gly  Ser  Gly  Gln  Tyr  Ser  Trp  Ile  Ile  Asn  Gly  Ile  Glu  Trp  Ala  Ile  Ala  Asn  Asn  Met
699  GTT  CTC  GGT  GCT  GAC  GGT  TCC  GGC  CAA  TAC  AGC  TGG  ATC  ATT  AAC  GGA  ATC  GAG  TGG  GCG  ATC  GCA  AAC  AAT  ATG

     120                                                 130                                                 140
     Asp  Val  Ile  Asn  Met  Ser  Leu  Gly  Gly  Pro  Ser  Gly  Ser  Ala  Ala  Leu  Lys  Ala  Ala  Val  Asp  Lys  Ala  Val  Ala
774  GAC  GTT  ATT  AAC  ATG  AGC  CTC  GGC  GGA  CCT  TCT  GGT  TCT  GCT  GCT  TTA  AAA  GCG  GCA  GTT  GAT  AAA  GCC  GTT  GCA

                                  150                                                 Ser  Thr  160
     Ser  Gly  Val  Val  Val  Val  Ala  Ala  Ala  Gly  Asn  Glu  Gly  Thr  Ser  Gly  Ser  Ser  Ser  Thr  Val  Gly  Tyr  Pro  Gly
849  TCC  GGC  GTC  GTA  GTC  GTT  GCG  GCA  GCC  GGT  AAC  GAA  GGC  ACT  TCC  GGC  AGC  TCA  AGC  ACA  GTG  GGC  TAC  CCT  GGT

     170                                                 180                                                 190
     Lys  Tyr  Pro  Ser  Val  Ile  Ala  Val  Gly  Ala  Val  Asp  Ser  Ser  Asn  Gln  Arg  Ala  Ser  Phe  Ser  Ser  Val  Gly  Pro
924  AAA  TAC  CCT  TCT  GTC  ATT  GCA  GTA  GGC  GCT  GTT  GAC  AGC  AGC  AAC  CAA  AGA  GCA  TCT  TTC  TCA  AGC  GTA  GGA  CCT

                                  200                                                 210
     Glu  Leu  Asp  Val  Met  Ala  Pro  Gly  Val  Ser  Ile  Gln  Ser  Thr  Leu  Pro  Gly  Asn  Lys  Tyr  Gly  Ala  Tyr  Asn  Gly
999  GAG  CTT  GAT  GTC  ATG  GCA  CCT  GGC  GTA  TCT  ATC  CAA  AGC  ACG  CTT  CCT  GGA  AAC  AAA  TAC  GGG  GCG  TAC  AAC  GGT

     220                                                 230                                                 240
     Thr  Ser  Met  Ala  Ser  Pro  His  Val  Ala  Gly  Ala  Ala  Ala  Leu  Ile  Leu  Ser  Lys  His  Pro  Asn  Trp  Thr  Asn  Thr
1074 ACG  TCA  ATG  GCA  TCT  CCG  CAC  GTT  GCC  GGA  GCG  GCT  GCT  TTG  ATT  CTT  TCT  AAG  CAC  CCG  AAC  TGG  ACA  AAC  ACT
```

FIG._1B - 2

FDE2TO: 08008260

```
                                    250 Gln                                                 260
     Gln  Val  Arg  Ser  Ser  Leu  Glu  Asn  Thr  Thr  Thr  Lys  Leu  Gly  Asp  Ser  Phe  Tyr  Tyr  Gly  Lys  Gly  Leu  Ile  Asn
1149 CAA  GTC  CGC  AGC  AGT  TTA  GAA  AAC  ACC  ACT  ACA  AAA  CTT  GGT  GAT  TCT  TTC  TAC  TAT  GGA  AAA  GGG CTG  ATC  AAC

     270                       275
     Val  Gln  Ala  Ala  Ala  Gln  OC                    TERM
1224 GTA  CAG  GCG  GCA  GCT  CAG  TAA  AACATAAAAAACCGGCCTTGGCCCCGCCGGTTTTTTATTTTTCTTCCTCCGCATGTTCAATCCGCTCC

1316 ATAATCGACGGATGGCTCCCTCTGAAAATTTTAACGAGAAACGGCGGGTTGACCCGGCTCAGTCCCGTAACGGCCAAGTCCTGAAACGTCTCAATCGCCG

1416 CTTCCCGGTTTCCGGTCAGCTCAATGCCGTAACGGTCGGCGGCGTTTTCCTGATACCGGGAGACGGCATTCGTAATCGGATC
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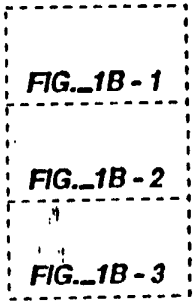
FIG._1B - 3

FIG._1B



CONSERVED RESIDUES IN SUBTILISINS FROM
*BACILLUS AMYLOLIQUEFACIENS*

```
1                   10                  20
A Q S V P . G . . . . A P A . H . . G

21                  30                  40
. T G S . V K V A V . D . G . . . . H P

41                  50                  60
D L . . . G G A S . V P . . . . . Q D

61                  70                  80
. N . H G T H V A G T . A A L N N S I G

81                  90                  100
V L G V A P S A . L Y A V K V L G A . G

101                 110                 120
S G . . S . L . . G . E W A . N . . . .

121                 130                 140
V . N . S L G . P S . S . . . . . A . .

141                 150                 160
. . . . . G V . V V A A . G N . G . . .

161                 170                 180
. . . . . Y P . . Y . . . . A V G A .

181                 190                 200
D . . N . . A S F S . . G . . L D . . A

201                 210                 220
P G V . . Q S T . P G . . Y . . . N G T

221                 230                 240
S M A . P H V A G A A A L . . . K . . .

241                 250                 260
W . . . Q . R . . L . N T . . . L G . .

261                 270
. . Y G . G L . N . . A A . .
```

FIG._2

EP 0 328 299 A2

COMPARISON OF SUBTILISIN SEQUENCES FROM:

*B.amyloliquefaciens*
*B.subtilis*
*B.licheniformis*
*B.lentus*

```
01                  10                  20                  30
A Q S V P Y G V S Q I K A P A L H S Q G Y T G S N V K V A V I D S G I D S S H P
A Q S V P Y G I S Q I K A P A L H S Q G Y T G S N V K V A V I D S G I D S S H P
A Q T V P Y G I P L I K A D K V Q A Q G F K G A N V K V A V L D T G I Q A S H P
A Q S V P W G I S R V Q A P A A H N R G L T G S G V K V A V L D T G I S T * H P

41                  50                  60                  70
D L K V A G G A S M V P S E T N P F Q D N N S H G T H V A G T V A A L N N S I G
D L N V R G G A S F V P S E T N P Y Q D G S S H G T H V A G T I A A L N N S I G
D L N V V G G A S F V A G E A Y N * T D G N G H G T H V A G T V A A L D N T T G
D L N I R G G A S F V P G E * P S T Q D G N G H G T H V A G T I A A L N N S I G

81                  90                  100                 110
V L G V A P S A S L Y A V K V L G A D G S G Q Y S W I I N G I E W A I A N N M D
V L G V S P S A S L Y A V K V L D S T G S G Q Y S W I I N G I E W A I S N N M D
V L G V A P S V S L Y A V K V L N S S G S G S Y S G I V S G I E W A T T N G M D
V L G V A P S A E L Y A V K V L G A S G S G S V S S I A Q G L E W A G N N G M H

121                 130                 140                 150
V I N M S L G G P S G S A A L K A A V D K A V A S G V V V V A A A G N E G T S G
V I N M S L G G P T G S T A L K T V V D K A V S S G I V V A A A A G N E G S S G
V I N M S L G G A S G S T A M K Q A V D N A Y A R G V V V V A A A G N S G N S G
V A N L S L G S P S P S A T L E Q A V N S A T S R G V L V V A A S G N S G A G S
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FIG._3A

EP 0 880 897 A2

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161                 170                 180                 190
S S S T V G Y P G K Y P S V I A V G A V D S S N Q R A S F S S V G P E L D V M A
S T S T V G Y P A K Y P S T I A V G A V N S S N Q R A S F S S A G S E L D V M A
S T N T I G Y P A K Y D S V I A V G A V D S N S N R A S F S S V G A E L E V M A
* * * * I S Y P A R Y A N A M A V G A T D Q N N N R A S F S Q Y G A G L D I V A

201                 210                 220                 230
P G V S I Q S T L P G N K Y G A Y N G T S M A S P H V A G A A A L I L S K H P N
P G V S I Q S T L P G G T Y G A Y N G T S M A T P H V A G A A A L I L S K H P T
P G A G V Y S T Y P T N T Y A T L N G T S M A S P H V A G A A A L I L S K H P N
P G V N V Q S T Y P G S T Y A S L N G T S M A T P H V A G A A A L V K Q K N P S

241                 250                 260                 270
W T N T Q V R S S L E N T T T K L G D S F Y Y G K G L I N V Q A A A Q
W T N A Q V R D R L E S T A T Y L G N S F Y Y G K G L I N V Q A A A Q
L S A S Q V R N R L S S T A T Y L G S S F Y Y G K G L I N V E A A A Q
W S N V Q I R N H L K N T A T S L G S T N L Y G S G L V N A E A A T R
```
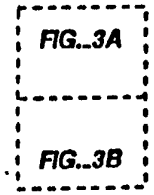

FIG._3B

FIG._3



FOE210 080894260

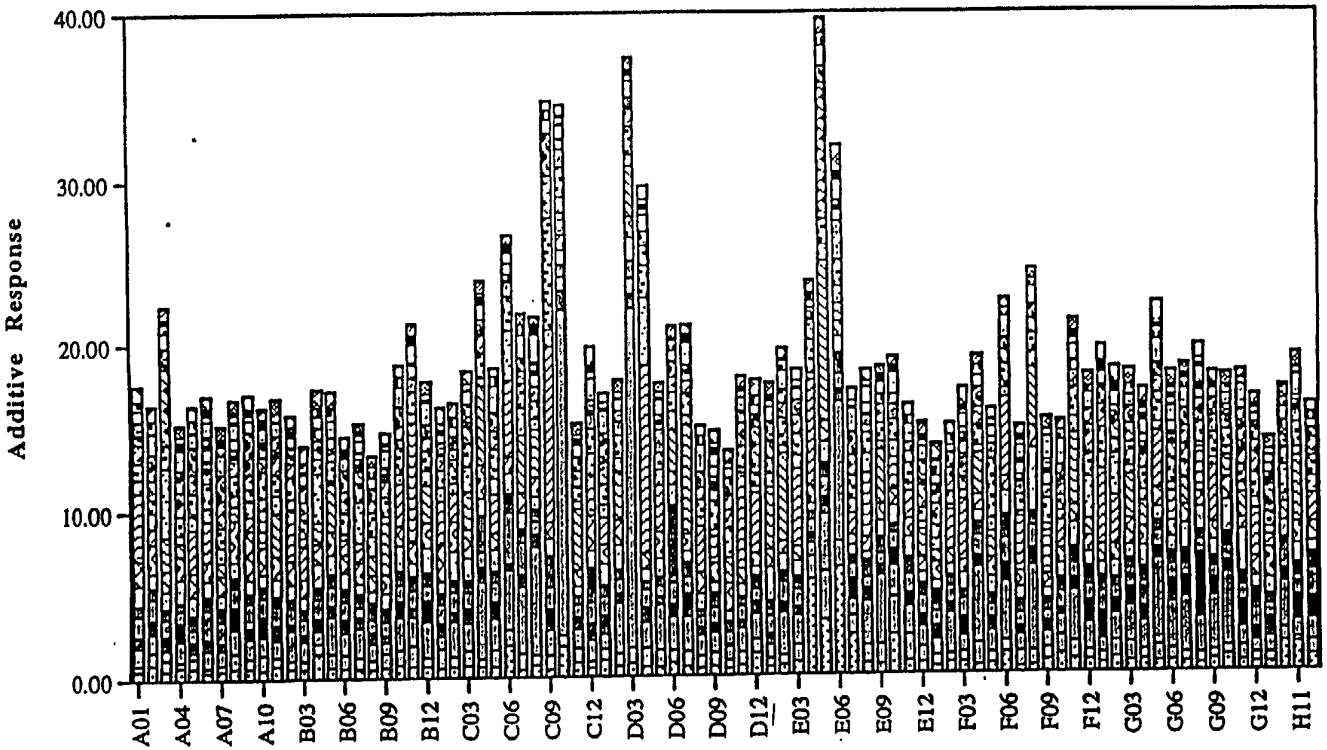



FIG. 4

EP 0 812 907 A2

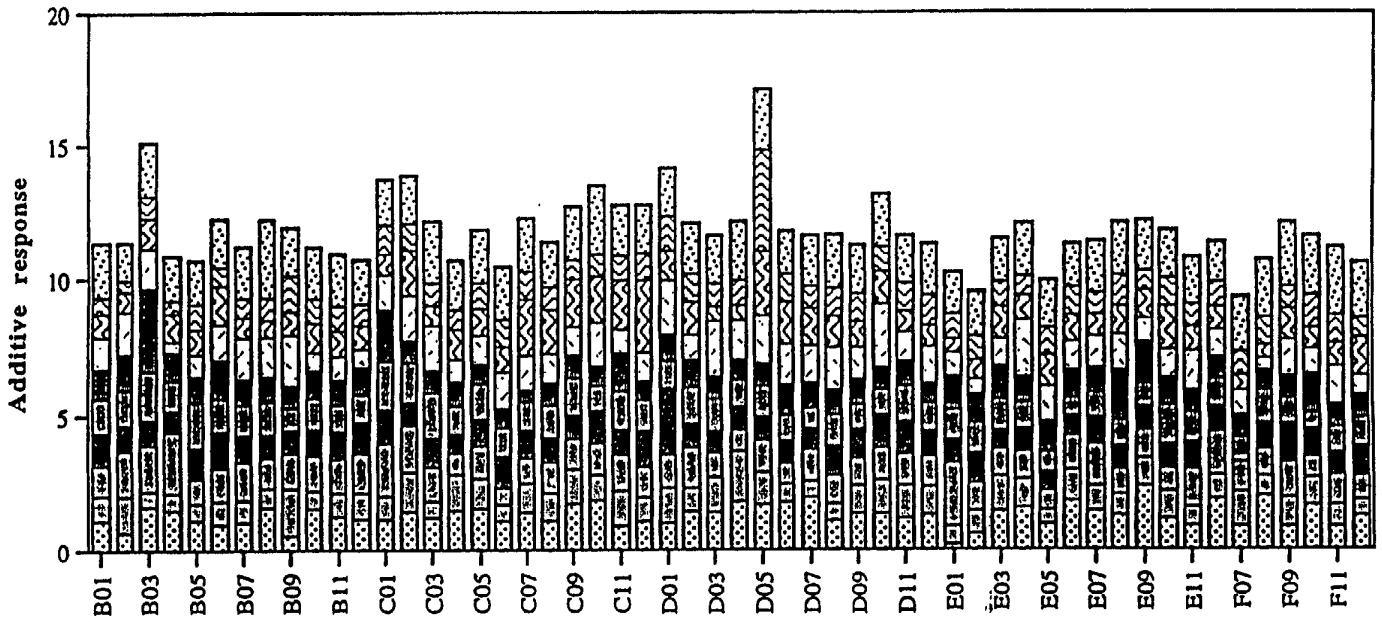



FIG. 5

| | | | | | |
|---|---|---|---|---|---|
| 1 | A12 | IKDFHVYFRESRDAG | 49 | E12 | SATSRGVLVVAASGN |
| 2 | A11 | LEQAVNSATSRGVLV | 50 | E11 | SRGVLVVAASGNSGA |
| 3 | A10 | AQSVPWGISRVQAPA | 51 | E10 | VLVVAASGNSGAGSI |
| 4 | A9 | VPWGISRVQAPAAHN | 52 | E9 | VAASGNSGAGSISYP |
| 5 | A8 | GISRVQAPAAHNRGL | 53 | E8 | SGNSGAGSISYPARY |
| 6 | A7 | RVQAPAAHNRGLTGS | 54 | E7 | SGAGSISYPARYANA |
| 7 | A6 | APAAHNRGLTGSGVK | 55 | E6 | GSISYPARYANAMAV |
| 8 | A5 | AHNRGLTGSGVKVAV | 56 | E5 | SYPARYANAMAVGAT |
| 9 | A4 | RGLTGSGVKVAVLDT | 57 | E4 | ARYANAMAVGATDQN |
| 10 | A3 | TGSGVKVAVLDTGIS | 58 | E3 | ANAMAVGATDQNNNR |
| 11 | A2 | GVKVAVLDTGISTHP | 59 | E2 | MAVGATDQNNNRASF |
| 12 | A1 | VAVLDTGISTHPDLN | 60 | E1 | GATDQNNNRASFSQY |
| 13 | B12 | LDTGISTHPDLNIRG | 61 | F12 | DQNNNRASFSQYGAG |
| 14 | B11 | GISTHPDLNIRGGAS | 62 | F11 | NNRASFSQYGAGLDI |
| 15 | B10 | THPDLNIRGGASFVP | 63 | F10 | ASFSQYGAGLDIVAP |
| 16 | B9 | DLNIRGGASFVPGEP | 64 | F9 | SQYGAGLDIVAPGVN |
| 17 | B8 | IRGGASFVPGEPSTQ | 65 | F8 | GAGLDIVAPGVNVQS |
| 18 | B7 | GASFVPGEPSTQDGN | 66 | F7 | LDIVAPGVNVQSTYP |
| 19 | B6 | FVPGEPSTQDGNGHG | 67 | F6 | VAPGVNVQSTYPGST |
| 20 | B5 | GEPSTQDGNGHGTHV | 68 | F5 | GVNVQSTYPGSTYAS |
| 21 | B4 | STQDGNGHGTHVAGT | 69 | F4 | VQSTYPGSTYASLNG |
| 22 | B3 | DGNGHGTHVAGTIAA | 70 | F3 | TYPGSTYASLNGTSM |
| 23 | B2 | GHGTHVAGTIAALNN | 71 | F2 | GSTYASLNGTSMATP |
| 24 | B1 | THVAGTIAALNNSIG | 72 | F1 | YASLNGTSMATPHVA |
| 25 | C12 | AGTIAALNNSIGVLG | 73 | G12 | LNGTSMATPHVAGAA |
| 26 | C11 | IAALNNSIGVLGVAP | 74 | G11 | TSMATPHVAGAAALV |
| 27 | C10 | LNNSIGVLGVAPSAE | 75 | G10 | ATPHVAGAAALVKQK |
| 28 | C9 | SIGVLGVAPSAELYA | 76 | G9 | HVAGAAALVKQKNPS |
| 29 | C8 | VLGVAPSAELYAVKV | 77 | G8 | GAAALVKQKNPSWSN |
| 30 | C7 | VAPSAELYAVKVLGA | 78 | G7 | ALVKQKNPSWSNVQI |
| 31 | C6 | SAELYAVKVLGASGS | 79 | G6 | KQKNPSWSNVQIRNH |
| 32 | C5 | LYAVKVLGASGSGSV | 80 | G5 | NPSWSNVQIRNHLKN |
| 33 | C4 | VKVLGASGSGSVSSI | 81 | G4 | WSNVQIRNHLKNTAT |
| 34 | C3 | LGASGSGSVSSIAQG | 82 | G3 | VQIRNHLKNTATSLG |
| 35 | C2 | SGSGSVSSIAQGLEW | 83 | G2 | RNHLKNTATSLGSTN |
| 36 | C1 | GSVSSIAQGLEWAGN | 84 | G1 | LKNTATSLGSTNLYG |
| 37 | D12 | SSIAQGLEWAGNNGM | 85 | H12 | TATSLGSTNLYGSGL |
| 38 | D11 | AQGLEWAGNNGMHVA | 86 | H11 | SLGSTNLYGSGLVNA |
| 39 | D10 | LEWAGNNGMHVANLS | 87 | H10 | STNLYGSGLVNAEAA |
| 40 | D9 | AGNNGMHVANLSLGS | 88 | H9 | NLYGSGLVNAEAATR |
| 41 | D8 | NGMHVANLSLGSPSP | | | |
| 42 | D7 | HVANLSLGSPSPSAT | | | |
| 43 | D6 | NLSLGSPSPSATLEQ | | | |
| 44 | D5 | LGSPSPSATLEQAVN | | | |
| 45 | D4 | PSPSATLEQAVNSAT | | | |
| 46 | D3 | SATLEQAVNSATSRG | | | |
| 47 | D2 | LEQAVNSATSRGVLV | | | |
| 48 | D1 | AVNSATSRGVLVVAA | | | |

FIG. 6A

| | | | | | |
|---|---|---|---|---|---|
| 1 | A12 | IKDFHVYFRESRDAG | 49 | E12 | KKIDVLNLSIGGPDF |
| 2 | A11 | DAELHIFRVFTNNQV | 50 | E11 | DVLNLSIGGPDFMDH |
| 3 | A10 | PLRRASLSLGSGFWH | 51 | E10 | NLSIGGPDFMDHPFV |
| 4 | A9 | RASLSLGSGFWHATG | 52 | E9 | IGGPDFMDHPFVDKV |
| 5 | A8 | LSLGSGFWHATGRHS | 53 | E8 | PDFMDHPFVDKVWEL |
| 6 | A7 | GSGFWHATGRHSSRR | 54 | E7 | MDHPFVDKVWELTAN |
| 7 | A6 | FWHATGRHSSRRLLR | 55 | E6 | PFVDKVWELTANNVI |
| 8 | A5 | ATGRHSSRRLLRAIP | 56 | E5 | DKVWELTANNVIMVS |
| 9 | A4 | RHSSRRLLRAIPRQV | 57 | E4 | WELTANNVIMVSAIG |
| 10 | A3 | SRRLLRAIPRQVAQT | 58 | E3 | TANNVIMVSAIGNDG |
| 11 | A2 | LLRAIPRQVAQTLQA | 59 | E2 | NVIMVSAIGNDGPLY |
| 12 | A1 | AIPRQVAQTLQADVL | 60 | E1 | MVSAIGNDGPLYGTL |
| 13 | B12 | RQVAQTLQADVLWQM | 61 | F12 | AIGNDGPLYGTLNNP |
| 14 | B11 | AQTLQADVLWQMGYT | 62 | F11 | NDGPLYGTLNNPADQ |
| 15 | B10 | LQADVLWQMGYTGAN | 63 | F10 | PLYGTLNNPADQMDV |
| 16 | B9 | DVLWQMGYTGANVRV | 64 | F9 | GTLNNPADQMDVIGV |
| 17 | B8 | WQMGYTGANVRVAVF | 65 | F8 | NNPADQMDVIGVGGI |
| 18 | B7 | GYTGANVRVAVFDTG | 66 | F7 | ADQMDVIGVGGIDFE |
| 19 | B6 | GANVRVAVFDTGLSE | 67 | F6 | MDVIGVGGIDFEDNI |
| 20 | B5 | VRVAVFDTGLSEKHP | 68 | F5 | IGVGGIDFEDNIARF |
| 21 | B4 | AVFDTGLSEKHPHFK | 69 | F4 | GGIDFEDNIARFSSR |
| 22 | B3 | DTGLSEKHPHFKNVK | 70 | F3 | DFEDNIARFSSRGMT |
| 23 | B2 | LSEKHPHFKNVKERT | 71 | F2 | DNIARFSSRGMTTWE |
| 24 | B1 | KHPHFKNVKERTNWT | 72 | F1 | ARFSSRGMTTWELPG |
| 25 | C12 | HFKNVKERTNWTNER | 73 | G12 | SSRGMTTWELPGGYG |
| 26 | C11 | NVKERTNWTNERTLD | 74 | G11 | GMTTWELPGGYGRMK |
| 27 | C10 | ERTNWTNERTLDDGL | 75 | G10 | TWELPGGYGRMKPDI |
| 28 | C9 | NWTNERTLDDGLGHG | 76 | G9 | LPGGYGRMKPDIVTY |
| 29 | C8 | NERTLDDGLGHGTFV | 77 | G8 | GYGRMKPDIVTYGAG |
| 30 | C7 | TLDDGLGHGTFVAGV | 78 | G7 | RMKPDIVTYGAGVRG |
| 31 | C6 | DGLGHGTFVAGVIAS | 79 | G6 | PDIVTYGAGVRGSGV |
| 32 | C5 | GHGTFVAGVIASMRE | 80 | G5 | VTYGAGVRGSGVKGG |
| 33 | C4 | TFVAGVIASMRECQG | 81 | G4 | GAGVRGSGVKGGCRA |
| 34 | C3 | AGVIASMRECQGFAP | 82 | G3 | VRGSGVKGGCRALSG |
| 35 | C2 | IASMRECQGFAPDAE | 83 | G2 | SGVKGGCRALSGTSV |
| 36 | C1 | MRECQGFAPDAELHI | 84 | G1 | KGGCRALSGTSVASP |
| 37 | D12 | CQGFAPDAELHIFRV | 85 | H12 | CRALSGTSVASPVVA |
| 38 | D11 | FAPDAELHIFRVFTN | 86 | H11 | LSGTSVASPVVAGAV |
| 39 | D10 | DAELHIFRVFTNNQV | 87 | H10 | TSVASPVVAGAVTLL |
| 40 | D9 | LHIFRVFTNNQVSYT | 88 | H9 | ASPVVAGAVTLLVST |
| 41 | D8 | FRVFTNNQVSYTSWF | 89 | H8 | VVAGAVTLLVSTVQK |
| 42 | D7 | FTNNQVSYTSWFLDA | 90 | H7 | GAVTLLVSTVQKREL |
| 43 | D6 | NQVSYTSWFLDAFNY | 91 | H6 | TLLVSTVQKRELVNP |
| 44 | D5 | SYTSWFLDAFNYAIL | 92 | H5 | VSTVQKRELVNPASM |
| 45 | D4 | SWFLDAFNYAILKKI | 93 | H4 | VQKRELVNPASMKQA |
| 46 | D3 | LDAFNYAILKKIDVL | 94 | H3 | RELVNPASMKQALIA |
| 47 | D2 | FNYAILKKIDVLNLS | 95 | H2 | VNPASMKQALIASAR |
| 48 | D1 | AILKKIDVLNLSIGG | 96 | H1 | ASMKQALIASARRLP |

FIG. 6B

| | | |
|---|---|---|
| 97 | I12 | IKDFHVYFRESRDAG |
| 98 | I11 | DAELHIFRVFTNNQV |
| 99 | I10 | KQALIASARRLPGVN |
| 100 | I9 | LIASARRLPGVNMFE |
| 101 | I8 | SARRLPGVNMFEQGH |
| 102 | I7 | RLPGVNMFEQGHGKL |
| 103 | I6 | GVNMFEQGHGKLDLL |
| 104 | I5 | MFEQGHGKLDLLRAY |
| 105 | I4 | QGHGKLDLLRAYQIL |
| 106 | I3 | GKLDLLRAYQILNSY |
| 107 | I2 | DLLRAYQILNSYKPQ |
| 108 | I1 | RAYQILNSYKPQASL |
| 109 | J12 | QILNSYKPQASLSPS |
| 110 | J11 | NSYKPQASLSPSYID |
| 111 | J10 | KPQASLSPSYIDLTE |
| 112 | J9 | ASLSPSYIDLTECPY |
| 113 | J8 | SPSYIDLTECPYMWP |
| 114 | J7 | YIDLTECPYMWPYCS |
| 115 | J6 | LTECPYMWPYCSQPI |
| 116 | J5 | CPYMWPYCSQPIYYG |

FIG. 6C

EP 2 527 450 A1

MKLVNIWLLLLVVLLCGKKHLGDRLEKKSFEKAPCPGCSHLTLKVEFSSTVVEYEYIVAFNGYFT
AKARNSFISSALKSSEVDNWRIIPRNNPSSDYPSDFEVIQIKEKQKAGLLTLEDHPNIKRVTPQR
KVFRSLKYAESDPTVPCNETRWSQKWQSSRPLRRASLSLGSGFWHATGRHSSRRLLRAIPRQVAQ
TLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERTNWTNERTLDDGLGHGTFVAGVIASM
RECQGFAPDAELHIFRVFTNNQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWEL
TANNVIMVSAIGNDGPLYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTWELPGGYGRMKPD
IVTYGAGVRGSGVKGGCRALSGTSVASPVVAGAVTLLVSTVQKRELVNPASMKQALIASARRLPG
VNMFEQGHGKLDLLRAYQILNSYKPQASLSPSYIDLTECPYMWPYCSQPIYYGGMPTVVNVTILN
GMGVTGRIVDKPDWQPYLPQNGDNIEVAFSYSSVLWPWSGYLAISISVTKKAASWEGIAQGHVMI
TVASPAETESKNGAEQTSTVKLPIKVKIIPTPPRSKRVLWDQYHNLRYPPGYFPRDNLRMKNDPL
DWNGDHIHTNFRDMYQHLRSMGYFVEVLGAPFTCFDASQYGTLLMVDSEEEYFPEEIAKLRRDVD
NGLSLVIFSDWYNTSVMRKVKFYDENTRQWWMPDTGGANIPALNELLSVWNMGFSDGLYEGEFTL
ANHDMYYASGCSIAKFPEDGVVITQTFKDQGLEVLKQETAVVENVPILGLYQIPAEGGGRIVLYG
DSNCLDDSHRQKDCFWLLDALLQYTSYGVTPPSLSHSGNRQRPPSGAGSVTPERMEGNHLHRYSK
VLEAHLGDPKPRPLPACPRLSWAKPQPLNETAPSNLWKHQKLLSIDLDKVVLPNFRSNRPQVRPL
SPGESGAWDIPGGIMPGRYNQEVGQTIPVFAFLGAMVVLAFFVVQINKAKSRPKRRKPRVKRPQL
MQQVHPPKTPSV

FIG. 7

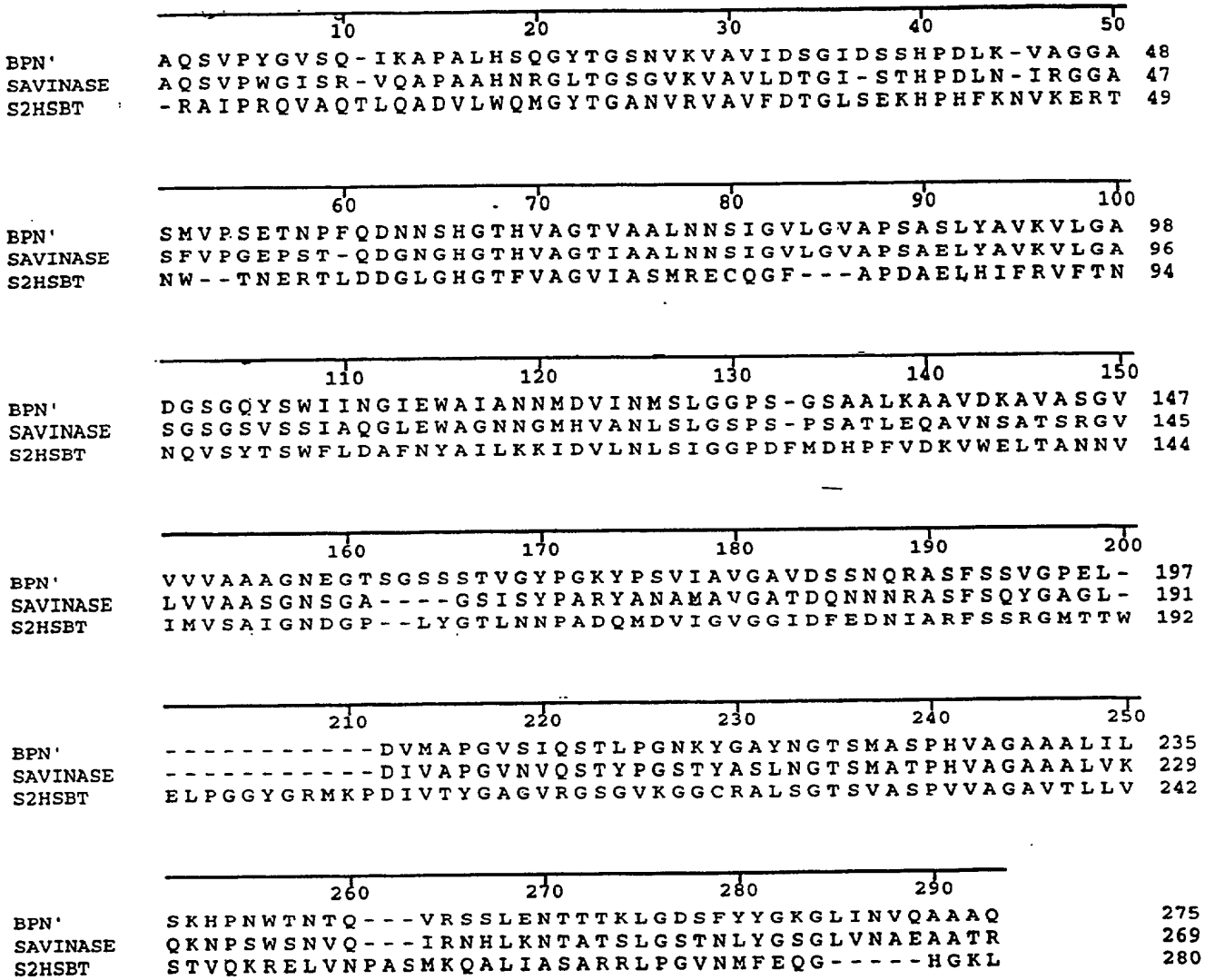

10 20 30 40 50
BPN' AQSVPYGVSQ-IKAPALHSQGYTGSNVKVAVIDSGIDSSHPDLK-VAGGA 48
SAVINASE AQSVPWGISR-VQAPAAHNRGLTGSGVKVAVLDTGI-STHPDLN-IRGGA 47
S2HSBT -RAIPRQVAQTLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERT 49
60 70 80 90 100
BPN' SMVPSETNPFQDNNSHGTHVAGTVAALNNSIGVLGVAPSASLYAVKVLGA 98
SAVINASE SFVPGEPST-QDGNGHGTHVAGTIAALNNSIGVLGVAPSAELYAVKVLGA 96
S2HSBT NW--TNERTLDDGLGHGTFVAGVIASMRECQGF---APDAELHIFRVFTN 94
110 120 130 140 150
BPN' DGSGQYSWIINGIEWAIANNMDVINMSLGGPS-GSAALKAAVDKAVASGV 147
SAVINASE SGSGSVSSIAQGLEWAGNNGMHVANLSLGSPS-PSATLEQAVNSATSRGV 145
S2HSBT NQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWELTANNV 144
160 170 180 190 200
BPN' VVVAAAGNEGTSGSSSTVGYPGKYPSVIAVGAVDSSNQRASFSSVGPEL- 197
SAVINASE LVVAASGNSGA----GSISYPARYANAMAVGATDQNNNRASFSQYGAGL- 191
S2HSBT IMVSAIGNDGP--LYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTW 192
210 220 230 240 250
BPN' ----------DVMAPGVSIQSTLPGNKYGAYNGTSMASPHVAGAAALIL 235
SAVINASE ----------DIVAPGVNVQSTYPGSTYASLNGTSMATPHVAGAAALVK 229
S2HSBT ELPGGYGRMKPDIVTYGAGVRGSGVKGGCRALSGTSVASPVVAGAVTLLV 242
260 270 280 290
BPN' SKHPNWTNTQ---VRSSLENTTTKLGDSFYYGKGLINVQAAAQ 275
SAVINASE QKNPSWSNVQ---IRNHLKNTATSLGSTNLYGSGLVNAEAATR 269
S2HSBT STVQKRELVNPASMKQALIASARRLPGVNMFEQG-----HGKL 280

FIG. 8

FOREIGN PATENT DOCUMENT

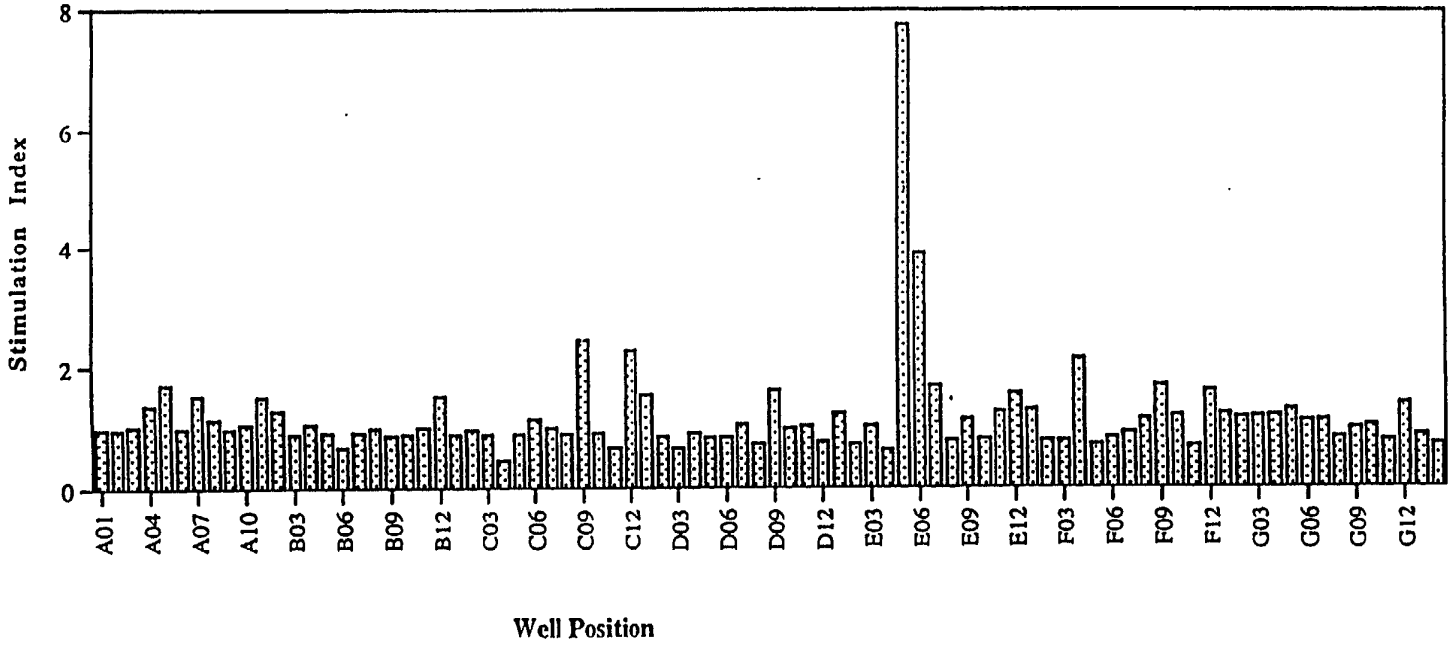



FIG. 9

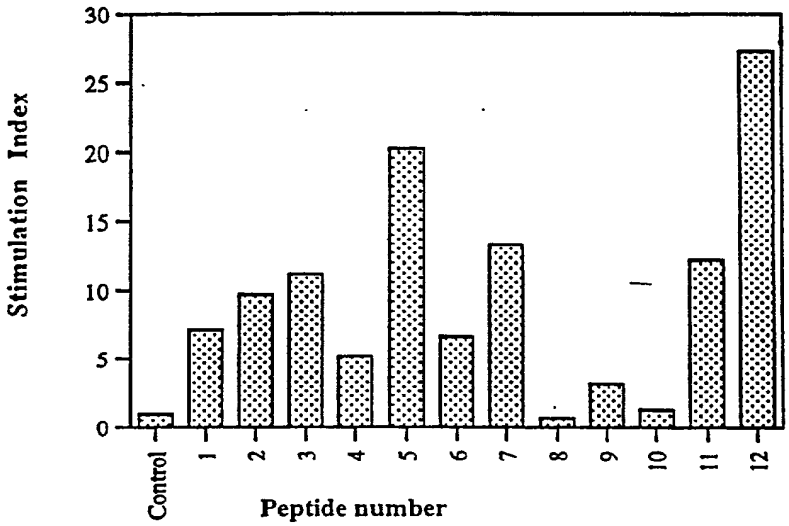
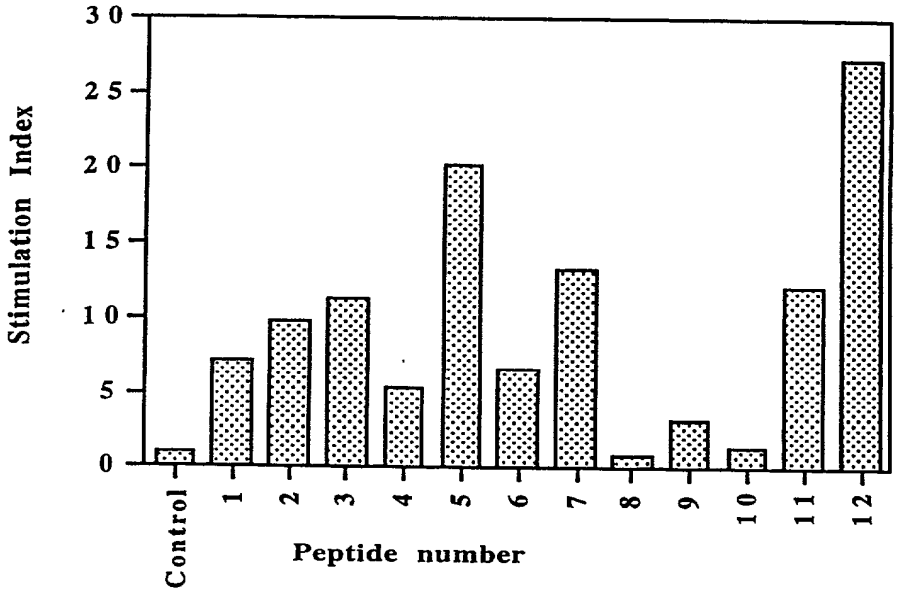

Stimulation Index
30
25
20
15
10
5
0
Control
1
2
3
4
5
6
7
8
9
10
11
12
Peptide number

FIG. 10




| Peptide number | Sequence |
|---|---|
| 1 (unmodified sequence) | GSISYPARYANAMAV |
| 2 | ASISYPARYANAMAV |
| 3 | GAISYPARYANAMAV |
| 4 | GSASYPARYANAMAV |
| 5 | GSIAYPARYANAMAV |
| 6 | GSISAPARYANAMAV |
| 7 | GSISYAARYANAMAV |
| 8 | GSISYPAAYANAMAV |
| 9 | GSISYPARAANAMAV |
| 10 | GSISYPARYAAAMAV |
| 11 | GSISYPARYANAAAV |
| 12 | GSISYPARYANAMAA |

FIG. 11

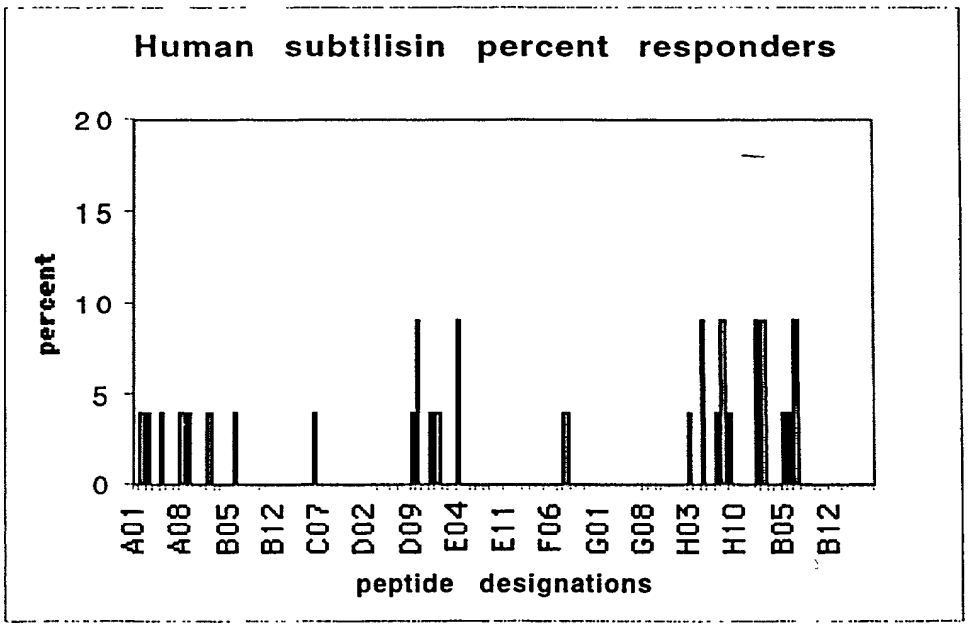

Human subtilisin percent responders
20
15
10
5
0
percent
A01
A08
B05
B12
C07
D02
D09
E04
E11
F06
G01
G08
H03
H10
B05
B12
peptide designations

FIG. 12

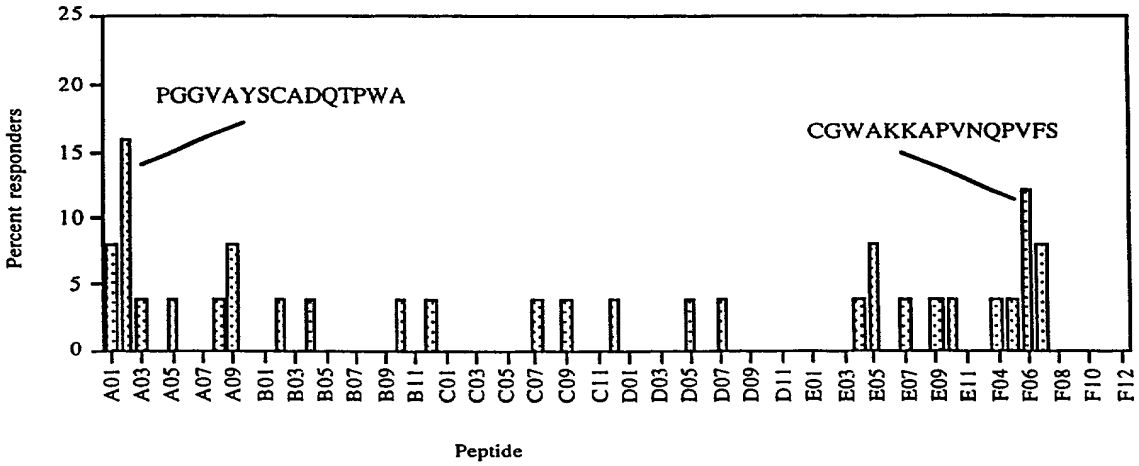

25
20
15
10
5
0
Percent responders
PGGVAYSCADQTPWA
CGWAKKAPVNQPVFS
A01
A03
A05
A07
A09
B01
B03
B05
B07
B09
B11
C01
C03
C05
C07
C09
C11
D01
D03
D05
D07
D09
D11
E01
E03
E05
E07
E09
E11
F04
F06
F08
F10
F12
Peptide

FIG. 13A

US 2002/0150950 A1 Oct. 17, 2002

```
          1          2          3          4          5
1234567890 1234567890 1234567890 1234567890 1234567890
MRSSPLLPSA VVAALPVLAL AADGRSTRYW DCCKPSCGWA KKAPVNQPVF
SCNANFQRIT DFDAKSGCEP GGVAYSCADQ TPWAVNDDFA LGFAATSIAG
SNEAGWCCAC YELTFTSGPV AGKKMVVQST STGGDLGSNH FDLNIPGGGV
GIFDGCTPQF GGLPGQRYGG ISSRNECDRF PDALKPGCYW RFDWFKNADN
PSFSFRQVQC PAELVARTGC RRNDDGNFPA VQIPSSSTSS PVNQPTSTST
TSTSTTSSPP VQPTTPSGCT AERWAQ
```

FIG. 13B

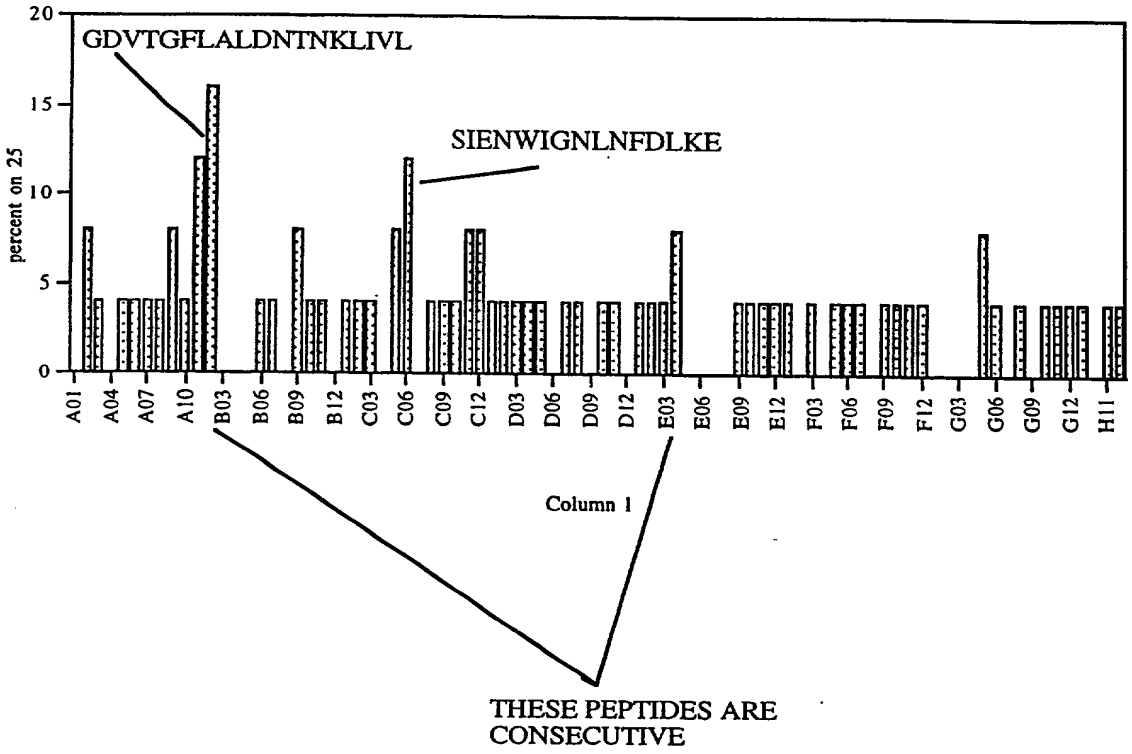

20
15
10
5
0
percent on 25
GDVTGFLALDNTNKLIVL
SIENWIGNLNFDLKE
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H11
Column 1
THESE PEPTIDES ARE CONSECUTIVE

FIG. 14A

```
  1 mrsslvlffv sawtalaspi rrevsqdlfn qfnlfaqysa aaycgknnda
 51 pagtnitctg nacpevekad atflysfeds gvgdvtgfla ldntnklivl
101 sfrgsrsien wignlnfdlk eindicsgcr ghdgftsswr svadtlrqkv
151 edavrehpdy rvvftghslg galatvagad lrgngydidv fsygaprvgn
201 rafaefltvq tggtlyrith tndivprlpp refgyshssp eywiksgtlv
251 pvtrndivki egidatggnn qpnipdipah lwyfgligtc l
```

FIG. 14B

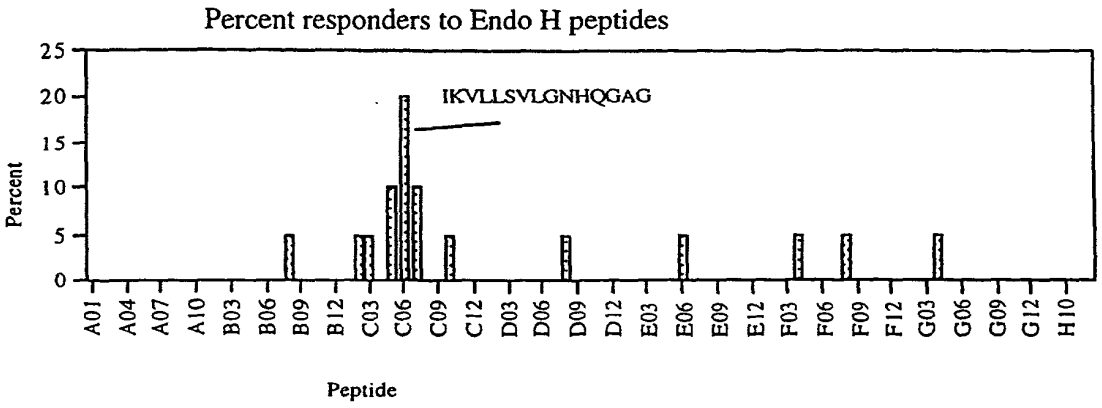

Percent responders to Endo H peptides
25
20
15
10
5
0
Percent
IKVLLSVLGNHQGAG
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H10
Peptide

FIG. 15A

```
  1 mftpvrrrvr taalalsaaa alvlgstaas gasatpspap apapapvkqg
 51 ptsvayvevn nnsmlnvgky tladgggnaf dvavifaani nydtgtktay
101 lhfnenvqrv ldnavtqirp lqqqgikvll svlgnhqqag fanfpsqqaa
151 safakqlsda vakygldgvd fddeyaeygn ngtaqpndss fvhlvtalra
201 nmpdkiisly nigpaasrls yggvdvsdkf dyawnpyygt wqvpgialpk
251 aqlspaavei grtsrstvad larrtvdegy gvyltynldg gdrtadvsaf
301 trelygseav rtp
```

**FIG. 15B**

BPN compiled for 22 individuals.

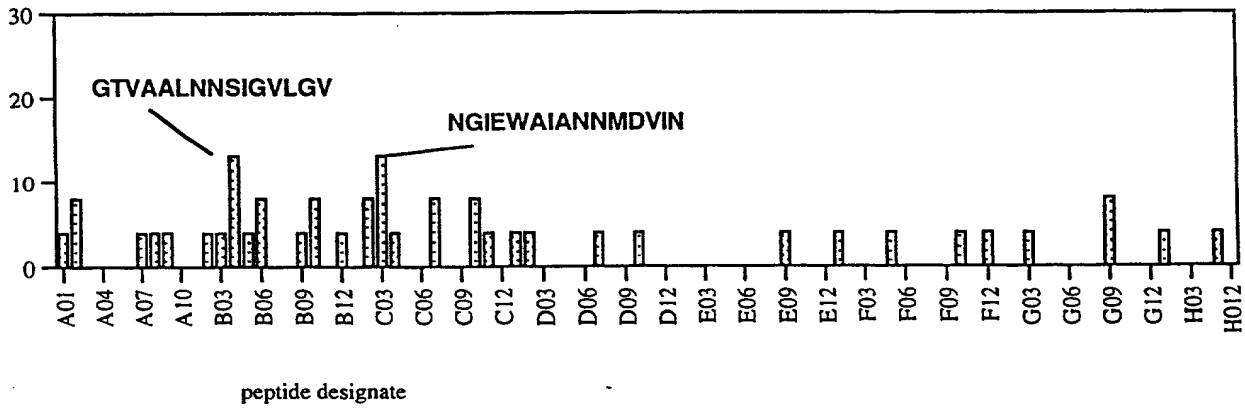



FIG. 16

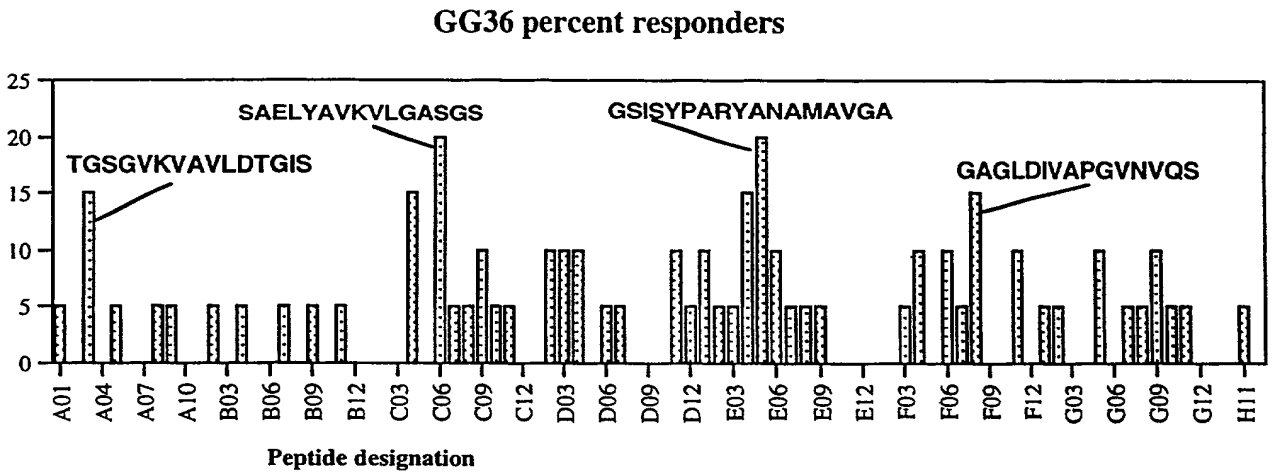

GG36 percent responders
Percent responders
25
20
15
10
5
0
TGSGVKVAVLDTGIS
SAELYAVKVLGASGS
GSISYPARYANAMAVGA
GAGLDIVAPGVNVQS
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H11
Peptide designation

FIG. 17

Hybrid enzyme sequence (GG36-BPN)

GG36

AQSVPWGISRVQAPAAHNRGLTGSGVKVAVLDTGISTHPDLNIRGGASFVPGEPSTQDGNGH

BPN

GTHVAGTIAALNNSIGVLGVAPSAELYAVKVLGASGSGSVSSIAQGLEWAGNNGMHVINMSLGGS

Δ

GSAALKAAVDKAVASGVVVVAAAGNEGTSGSSSTVGYPGKYPSVIAVGAVDSSNQRASFSSVGP

ELDVMAPGVSIQSTLPGNKYGAYNGTSMASPHVAGAAALILSKHPNWTNTQVRSSLENTTTKLGD

SFYY GKGLINVQAAAQ

FIG. 18

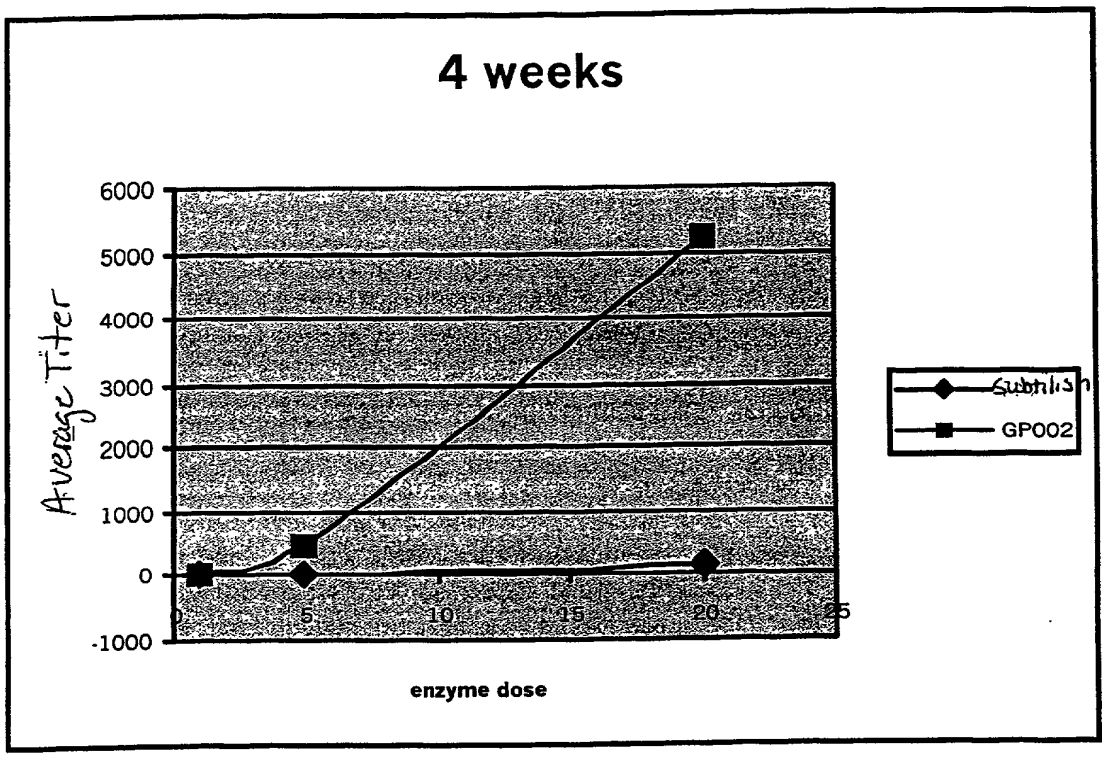

4 weeks
Average Titer
6000
5000
4000
3000
2000
1000
0
-1000
0
5
10
15
20
25
enzyme dose
Subtilisin
GP002

FIGURE 19A

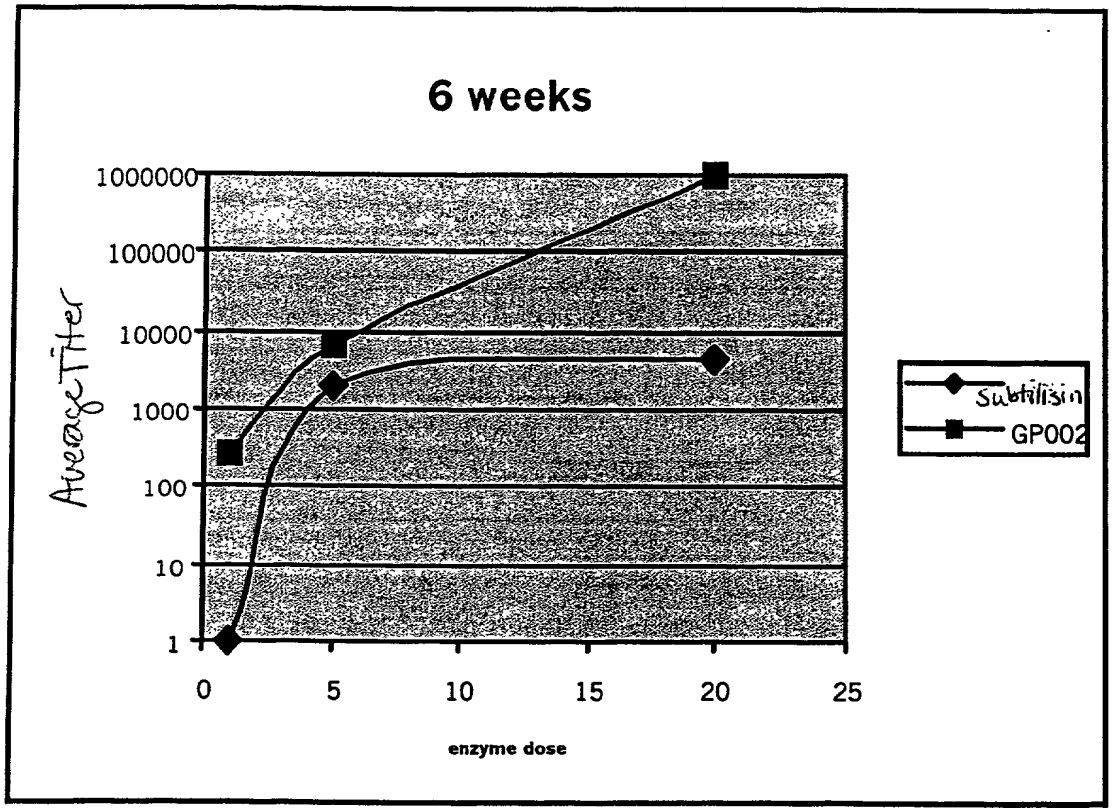

6 weeks
1000000
100000
10000
1000
100
10
1
Average Titer
0
5
10
15
20
25
enzyme dose
Subtilisin
GP002

FIGURE 19B

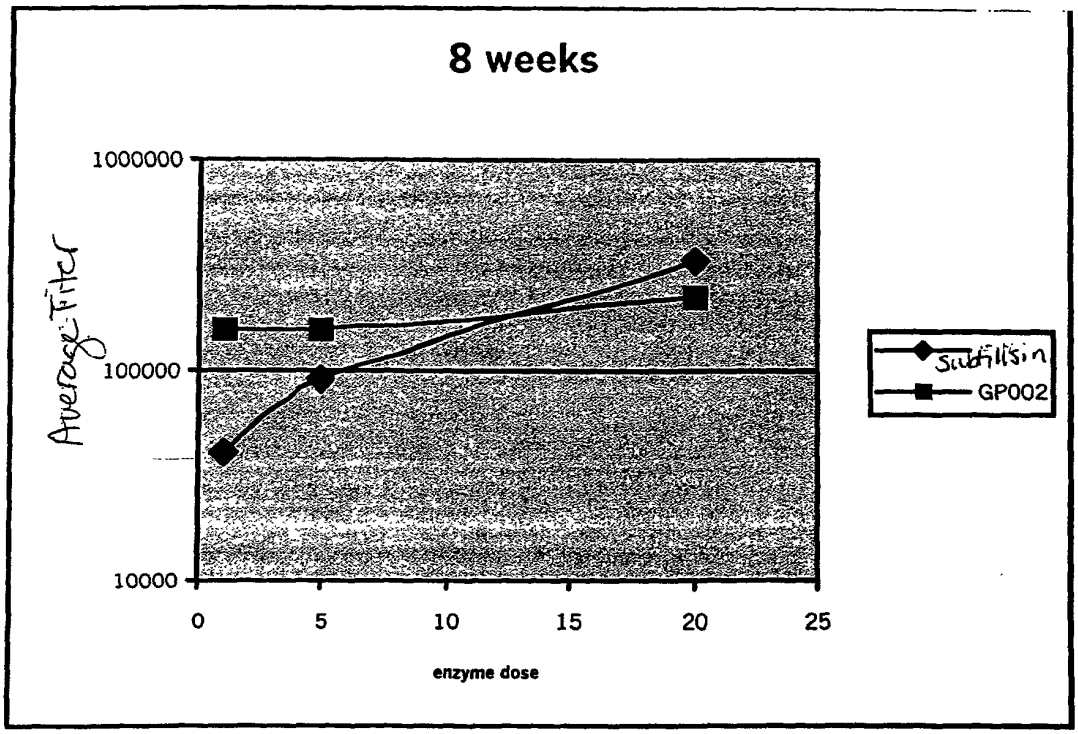

8 weeks
1000000
100000
10000
Average Titer
0
5
10
15
20
25
enzyme dose
Subtilisin
GP002

FIGURE 19C

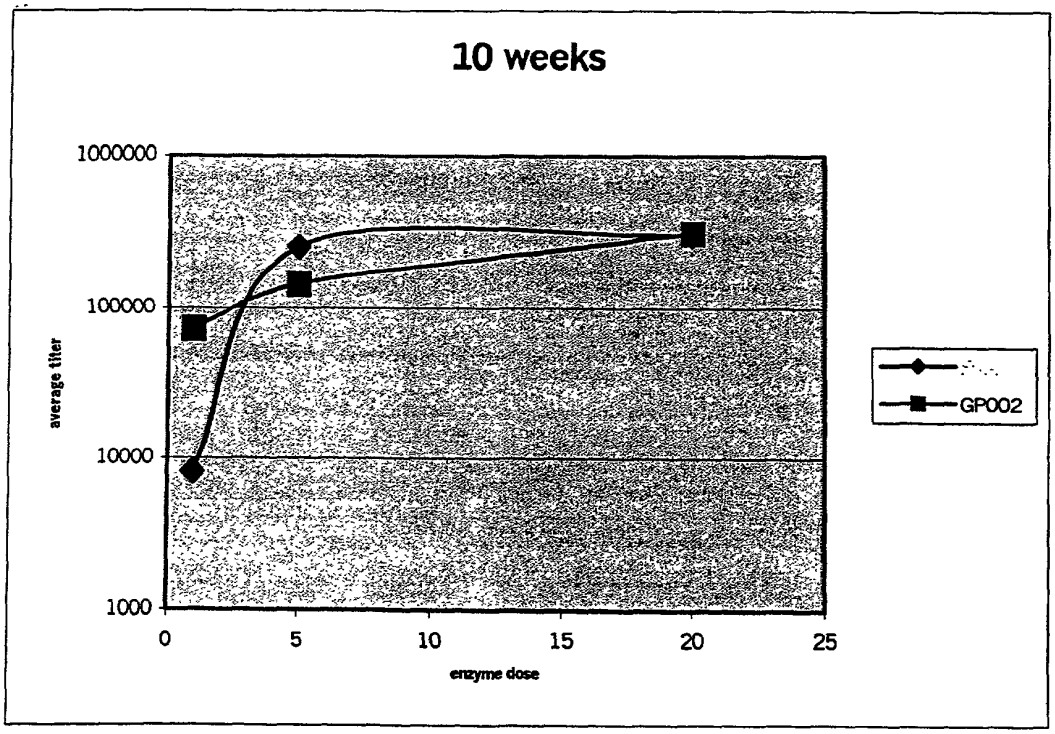

10 weeks
1000000
100000
10000
1000
average titer
0
5
10
15
20
25
enzyme dose
GP002

FIGURE 19D

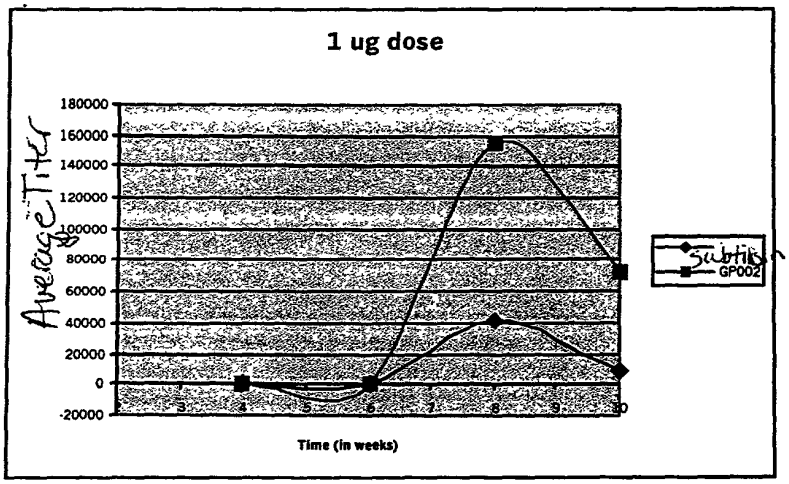

1 ug dose
Average Titer
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
3
4
5
6
7
8
9
10
Time (in weeks)
GP002

FIGURE 20A

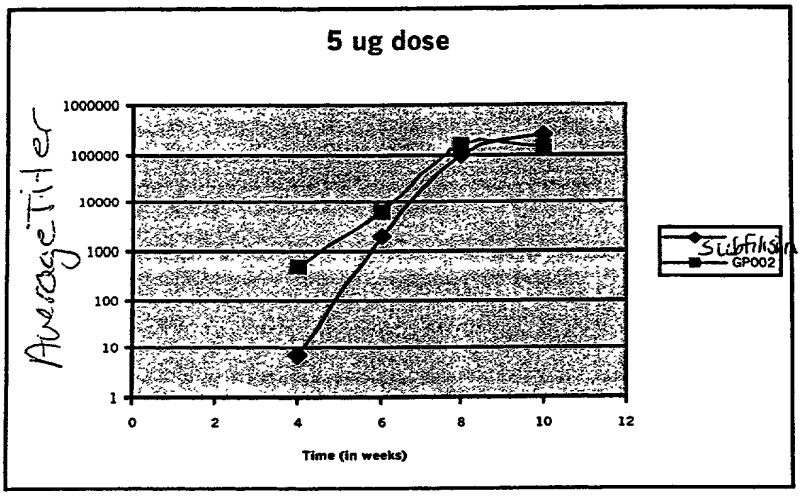

5 ug dose
Average Titer
1000000
100000
10000
1000
100
10
1
0
2
4
6
8
10
12
Time (in weeks)
GP002

FIGURE 20B

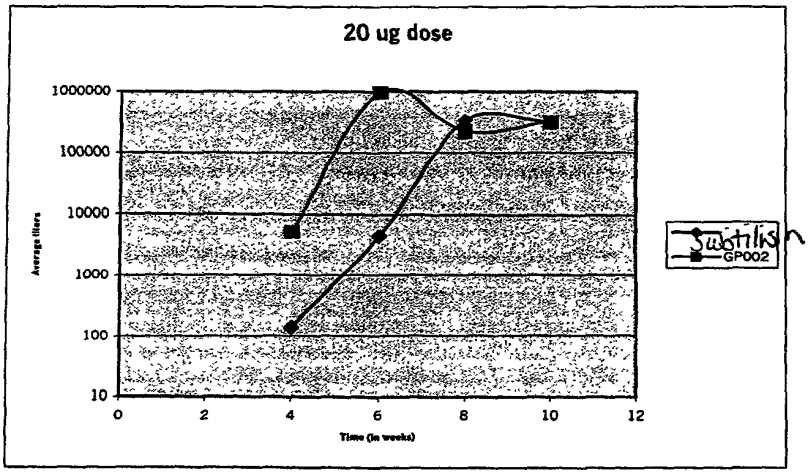

20 ug dose
1000000
100000
10000
1000
100
10
0
2
4
6
8
10
12
Average titers
Time (in weeks)
GP002

FIGURE 20C

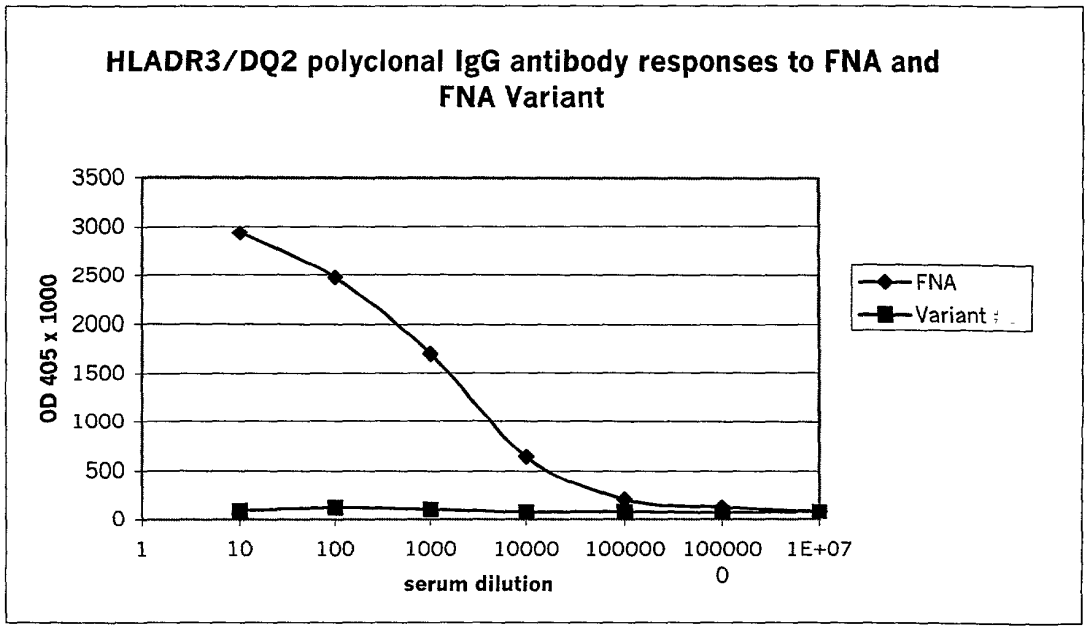

HLADR3/DQ2 polyclonal IgG antibody responses to FNA and FNA Variant
OD 405 x 1000
3500
3000
2500
2000
1500
1000
500
0
1
10
100
1000
10000
100000
1000000
1E+07
serum dilution
FNA
Variant

FIGURE 21